

GENETIC ENGINEERING, OR THE AMELIORATION OF GENETIC DEFECT

FEW SUBJECTS pose as many difficulties for rational discussion as does the bearing of genetic research on human welfare. It is monotonously coupled with such inflammatory themes as racism, the decline of the species, overpopulation, hidden genocide, religious debates on abortion and contraception, the plight of the individual in mass society, and "how many generations of idiots is enough." Apart from these clichés of social controversy, we also face serious problems in clarifying the technical context in a field where scientific innovations have far outpaced their technical application and applicability to man. Should we spend much time worrying about the ethical implications of the genetic findings of the next century, when we must do this on the basis of a set of assumptions about the human condition that will surely change dramatically in every other way?

The gap between elementary principle and practical realization poses many dilemmas for a fair-minded evaluation, and a brief commentary cannot do justice to all of the relevant issues. The scientist who concentrates on exposing the technical possibilities will be castigated for ignoring the ethical implications; and, if he goes further afield, he will be accused of sermoning, and indeed may be overreaching his particular area of competence.

According to journalistic accounts, we will shortly be writing prescriptions for human quality to order. "Do you want your baby to be eight feet tall, or have four hands? Just tell the geneticist, and he will arrange it for you," goes this line of advertisement. But the most sophisticated geneticist today is baffled by challenges such as Huntington's disease. Will the son of an afflicted father be afflicted later in life? What can he do to assure that his own children will not have it?

Perhaps some year soon we will know enough at least to recognize the genotype before neuronal degeneration has been irreversibly set in motion. But our failure to be able to provide significant help today is a humbling reality next to the effusive (though justifiable) predictions about future accomplishments.

What then of the bold claims for a brave new world of genetic manipulation? Their substance is grounded on the recent solution of many fundamental mysteries of genetic biochemistry. Many of the obstacles to genetic engineering, apart from the moral and political questions that may be posed, are technological; which is to say that their solution is consistent with our basic

scientific knowledge of the gene. But this is as if to say that "merely technical obstacles" prevent building a land bridge from San Francisco to Honolulu. It is safe to predict that this enterprise will never eventuate—not merely because it would be a million times more costly than previous bridges but, rather, because other challenges will compete for the energies and resources. And the presumed benefits will be achieved by other routes: the image of the trans-Pacific bridge will persist as a metaphor, reminding us of technical achievements in other fields of transport and communication and of the political prodigy of the evolution of a Pacific island from dependency to statehood.

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Construction works, like bridges, are open to evaluation and judgment by common sense widely shared. Biotechnical projects are more likely to be cloaked in an esoteric jargon that defeats common sense justification. We may then hear the most absurd generalization, such as "whatever is technically feasible tends to get done."

Anyone who has actually labored to "do" *anything* knows that the more appropriate slogans are: "almost nothing ever gets done, especially if it costs money"; or, "when a need is generally perceived, articulately formulated and wisely analyzed, the technical problems will be surmounted. But this will happen much sooner if a mass advertising campaign can be built around it." If* transoceanic bridges become fashionable (as might happen incidentally to an arms race), they will be built, and probably the same can be said for genetic engineering. Our foresight about the future will prove to be right or wrong more on the basis of the predictability of fashion than of the scientific basis to technical solutions. I do not venture to foresee the directions that

* Computereze for "if, and only if."

such fashion may take. This is more the realm of the political theorists or of authors such as John Brunner ("Stand on Zanzibar").

Where then does the scientist fit into such a discussion?

He can fairly justify his life and work in terms of fundamental knowledge about nature. Studies on the implantation of nuclei into eggs of different genotypes are a rewarding approach to learning how genes function and how this relates to how the egg develops. Were they done for the purported purpose of learning the technology of cloning in man, we would then be obliged to set a priority (positive or negative) on it from the standpoint of the human values that might justify or repudiate the investment. A small amount of "scientific" effort is, unhappily, biased by the expectation of the publicity that will attach to spectacular demonstrations of "behavior control," or "gene control," or "moon-walking" for its own sake; the scientific community can seek to impose criteria of *scientific* validity for the funding of such projects; or, failing this, to dissociate itself from the responsibility when (as is customary) it does not have the authority to make the critical decisions.

Alternatively, the scientist can function as the actual or effective member of a technological team that will address itself to the solution of grave problems that encumber human welfare. Then we must and usually do insist that the problems are real ones and that technical solutions are credible. What is more often obscured is the need to examine all the side effects, to inhibit the premature exploitation of new cures that may be far worse than the disease, to assure that as much sophistication goes into looking for the side effects as was eagerly purchased for the primary solution. The hazards of suboptimal solutions are well appreciated for drugs; but we are just now feeling their full force in such disparate fields as pesticides and auto transport. Pesticide-poisoning and air pollution have been figured as technological jinn. It would be fairer to lay the blame on technological idiocy and the refusal to make the economic investments needed to develop all the science required for the safe and healthful utilization of the new tricks.

What then are the *problems* to which genetic science can be applied? Some may think of rescuing man from the prospect of nuclear annihilation by recasting the genes for aggression—or acquiescence—that are supposed to predestine a future of territorial conflict. Even if we postulate for sake of argument that we know the genetics of militarism, we have no way to apply it without solving the political problem that is the primary difficulty to begin with. If we could agree upon applying genetic (or any other effective) remedies to global problems in the first place, we probably would need no recourse to them in the actual event.

The converse argument applies to the gloomier predictions of totalitarian abuse of a genetic technology. The scenario of Brave New World is well advertised by now, and no one doubts that a modern slave state would reinforce its class stratification by genetic con-

trols. But it could not do so without having instituted slavery in the first place, for which the control of the mass media presents much more immediate dangers than knowledge of DNA. It is indeed true that I might fear the control of my behavior through electrical impulses directed into my brain, but (possibly excepting television) I do not accept the implantation of the electrodes except at the point of a gun: the gun is the problem.

So much for the grand designs of genetic engineering. There remain the very real tragedies of genetic disease. The societal interest in preventing or ameliorating mental retardation and other forms of congenital malformation is obvious. (The true cost of lifetime maintenance of a 21-trisomy approaches a megadollar). It is also entirely congruent with the needs of the family and, if we believe in the nobility of man and the worth of *human* life, also of the afflicted child as well.

The most effective avenues of preventing genetic disease include (1) the primary prevention of gene mutations, and (2) the detection and humane containment of the DNA lesions once introduced into the gene pool. The "natural" mutation process in man results in the introduction of a new bit of genetic misinformation once in every ten gametes. Most of the human cost of this "mutational load" is paid during early stages of fertilization and pregnancy, where it makes up a fair part of the total fetal wastage. But about 2 per cent of newborns suffer from a recognizable discrete genetic defect. This is just the tip of the iceberg; the heritability of many common diseases suggests that from one-fourth to one-half of *all* disease is of genetic origin, for there are important variations in susceptibility to the frankest of environmental insults.

Not all of this health deficit can be attributed to recurrent mutations. An unknown proportion results from the selective advantage that is paradoxically associated with the heterozygous state of many genes, even some with lethal effect in the homozygote (such as sickle-cell hemoglobin). Nevertheless, a significant part of medicine—much more than most practitioners overtly recognize—is in fact directed to lesions that are inherently preventable, if we could control the mutation process in the background.

About a tenth of the "natural mutation rate" can be attributed to background radiation—from cosmic rays and from radioactive potassium and other isotopes in our natural environment. Therefore, doubling the background, which would correspond to the "maximum permissible standards" now advocated by federal agencies, would add another 10 per cent to the existing mutation rate: one-ninth rather than one-tenth of our gametes would carry deleterious mutations. This is an enormous impact in absolute terms; a modest increase in relative terms. We must, nevertheless, pay careful attention to the benefits that would be connected with this level of radiation exposure to be sure we are getting a fair bargain.

It must be pointed out that industrial nuclear energy activities today add less than 10 per cent to the average background (hence, less than 1 per cent to the muta-

tion rate); medical x-rays add 50 per cent and 5 per cent, respectively. The same question applies: the now-more-prevalent standards for the judicious and cost-effective use of diagnostic x-rays do not necessarily or automatically excuse the dispensable residue.

A significant portion of "spontaneous" mutations must be attributed to environmental chemicals, many of which are clearly established as mutagens in laboratory experiments (for example, the peroxy compounds that characterize smog). The extent to which such materials reach the germ cells is absolutely unknown at present. There are good reasons to believe, however, that (1) the induction of mutations, in germ cells and of cancer and in somatic cells, are fundamentally similar processes—most chemical carcinogens being also mutagenic when properly tested; and (2) a large part of the incidence of cancer is of chemical-environmental origin, cigarette-smoking being only the best-known and best-advertised example. It therefore follows that environmental mutagenesis is equally prevalent. If the relative effects of radiation in the two systems are any hint, the cryptic penalties of the mutations are likely, in the long run, to exact even a larger price in human misery than the short run cancers.

The direct observation of human populations for evidence of changes in mutation rates is an almost hopeless task. We have no way of managing the tangle of known and unknown environmental influences that bear on different individuals. Nor do we have tractable assays for the occurrence of new mutations, whose manifestation may be delayed (by transmission through heterozygotes) for many generations, or confused with malformations due to pre-existing mutant genes, or to non-genetic causes. If we had to rely upon epidemiological evidence, we would still lack persuasive evidence that radiation, even in barely sub-lethal doses, was mutagenic in man.

Our only recourse is the laboratory experiment, with a convenient mammal such as the mouse, and sometimes even more efficiently with viruses and micro-organisms. Even so, only the most potent mutagens can be identified with mice, and many uncertainties will remain that cannot be resolved given possible differences in metabolism and transport, cell selection, intrinsic sensitivity, and the duration and style of life of the human versus the experimental species. Very recently, we have been able to look deeper into the mechanism of chemical mutation, at the level of the structure and repair of the DNA molecule, and new procedures may be developed that can give us more reliable information on the susceptibility of the DNA of human cells to environmental insults. They may also give us clues to ways of neutralizing mutational lesions, either by blocking the primary effects of mutagens on DNA or by bolstering the natural mechanisms of "editing" and repair of DNA information.

Once a mutation has been allowed to occur in a gamete, and this then participates in fertilization and the production of a new individual, we face a much more difficult problem in any effort at genetic hygiene. For now we must deal with the destinies of human indi-

viduals, not merely the chemistry of an isolated segment of DNA. Our problem, seen in the large, is compounded by every humanitarian effort to compensate for a genetic defect, insofar as this shelters the carrier from natural selection. So it must be accepted that medicine, even prenatal care (which may permit the fragile fetus to survive), already intrudes on the question "Who shall live?," the challenge so often thrust at rational discussions of policies that might influence the frequencies of deleterious genes. It is so difficult to do only good in such matters that we are best off putting our strongest efforts into the prevention of mutations, so as to minimize the heavy moral and other burdens of decision once the gene pool has been seeded with them.

We still cannot evade an evolutionary legacy of genetic damage that would remain with us for generations, even if all new mutation could be stopped by fiat. Our fundamental resources remain very feeble: in a few cases, we can diagnose the heterozygous carriers of recessive mutations, and the genetic counselor can then advise the prospective parents of the odds that they will have affected children. Where voluntary childlessness is unacceptable, it is also sometimes possible to monitor a pregnancy by sampling cells from the amniotic fluid. This can then enable the mother to proceed with confidence, or to request an elective abortion, on the basis of firm knowledge of the genotype of the fetus. We can expect a rapid extension of technical facilities for such diagnoses. At present, they are limited to examination of the chromosomes (for gross chromosomal abnormalities, such as Down's syndrome), and to enzyme assays on cultured cells, which can diagnose a few dozen rare diseases with varying degrees of reliability. We will surely be learning, during the next decade, how to use much more sophisticated approaches to the structure of the DNA and RNA of such cells for more basic diagnostic methods.

In many cases, a deeper understanding of the causal chain by which a DNA alteration leads to pathology may help us devise new forms of therapy to compensate for the genetic defect. This may be as crude as the use of insulin in diabetes, or as subtle as the use of controlled diets in phenylketonuria. (Both approaches are valuable; neither is entirely satisfactory.)

Another approach to constructive therapy, which may mitigate a variety of diseases, is an extension of the existing uses of specific virus strains. At present, their role in medicine is confined to their use as vaccines, for the provocation of immunity against related, wild viruses. This is a specialized example of the modification of cell metabolism by inoculated DNA, discovered empirically by Jenner, and still quite imperfectly understood (our ignorance being concealed by the conceptualizations of clinical virology which still fail to explain just how a vaccine works—e.g., to state just which cells of the vaccinated individual are carrying the viral genetic information, and in what form). We can visualize the engineering of other viruses so that they will introduce compensatory genetic information into the appropriate somatic cells, to restore functions that

are blanked out in a given genetic defect. As with vaccine viruses, this presumably will leave the germ cell DNA unaltered, and therefore does not attack the defective gene as such. If we can cope with the disease, should we bother about the gene? Or may we not leave that problem to another generation?

There has been much to-do about another theoretical possibility—"cloning" a man, as might be done by the renucleation of a fertilized egg with a somatic cell nucleus from an existing individual. Similar experiments have been successfully completed with frogs and are being attempted with mice. Such experiments, with laboratory animals, will surely be very fruitful of basic scientific knowledge if the technique can be developed. It would also have enormous value in livestock breeding, just as cloning (propagation by cuttings) is a mainstay of horticulture. Until such experiments have been pursued in some depth, with other animals, it is merely a speculative game to discuss applying such reproductive novelties to man. There is no urgent social problem to be addressed by such a technique. It does serve as a metaphor to indicate that future generations will have infinitely more powerful ways than we do to deal with whatever they perceive as [the] socially urgent issues of human nature. We can therefore focus, more confidently, on dealing with the distress of individual human beings in the immediate generation. The cloning issue shows that intrusive genetic engineering, if it is pursued for any other reason, will have plenty of policy problems to digest even before the "technology" has reached the point of detailed synthesis of genotypes by design.

Finally, medical scientists in general well appreciate and usually respond to ethical concerns about the application of new techniques in man, by contrast to

experimental animals. For a long time, it has been known that one could operate on the brain, in such "interesting" ways as dividing the corpus callosum, with the possibility of the development of autonomous "intellects" in the two hemispheres. It would be unthinkable to apply such surgical technology to man without the persuasion and conviction that it would be for the benefit of the patient-subject. We will not be given the benefit of the doubt in public discussions of such questions; there are many influential people who really believe that "anything feasible will be done," and we may have to restate the obvious many times in reviewing the ethical constraints on possible experimentation.

To return to the "clone-a-man" metaphor: in my view, we simply do not know enough about the question, at either a technical or an ethical level (and these are intertwined), to dogmatize about whether or not it should ever be done. Certainly it cannot be thought of, within the framework of our generally-accepted standards of medical ethics, unless (1) we can make and communicate a reasonably confident prediction of the outcome, and, more important, (2) it has the informed consent, and serves a reasonable humanitarian purpose, of and for the individuals who are involved. In genetic matters, this must include the interests of the prospective newborn, as well as of his parents, and of the community. If we demand that he be represented in person, then no one could reasonably be allowed to be born, whether by "natural" sexual fertilization, by the design of his parents, or otherwise. The specific question of "cloning-a-man" is almost the least important one I can think of; the one it opens up—who must be held to account for the next generation, and how—may be the most.